-O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -$N(R^8)$-, -$C(O)NR^8$-, -$OC(O)N(R^8)$-, -$CSN(R^8)$-, -$N(R^8)CO$-, -$N(R^8)C(O)O$-, -$N(R^8)CS$-, -$S(O)_2N(R^8)$-, -$N(R^8)S(O)_2$-, -$N(R^8)CON(R^8)$-, -$N(R^8)CSN(R^8)$-, and -$N(R^8)SO_2N(R^8)$-;

r is zero or the integer 1;

R is a carboxylic acid (CO_2H), or an ester group or amide group;

and the salts, solvates, hydrates and N-oxides thereof;

with the provisos that:

(1) when Ar^1 is unsubstituted phenyl, r is zero, L^1 is C(O)O, Ar^2 is unsubstituted 1, 4-phenylene or 1,4-phenylene substituted with 3-fluoro, R^a and $R^{a'}$ are hydrogen, R is CO_2H, and R^1 is $NHCOR^3$, then R^3 is other than unsubstituted phenyl;

(2) when r is zero, L^1 is -O-, Ar^2 is 1,3-phenylene substituted with 4-methoxy, R^a and $R^{a'}$ are hydrogen, and R is CO_2CH_3, R^1 is $NHCOR^3$, R^3 is tert-butyloxy, then Ar^1 is other than phenyl substituted in the 4-position with 3-methoxy-3-oxo-1-propenyl; and

(3) when Ar^1 is phenyl substituted in the 4-position with methoxy, r is zero, L^1 is -O-, R^1 is $NHCOR^3$, R^3 is methyl, R^a and $R^{a'}$ are hydrogen, and R is CO_2Et, then Ar^2 is other than 3,5-dinitro or 3,5-diiodo substituted.

REMARKS

Reconsideration of the present application in view of the above amendments and following remarks is requested respectfully.

Claims 2 to 22 are pending. Claim 16 has been amended. The present Office Action includes rejections under 35 U.S.C. §§§101, 102, and 112, first and second paragraph, which are discussed in detail below.

Discussion of the Rejections Under Section 102

Claims 3, 4, 7, 9, 10, 12, and 16 have been rejected as being anticipated in view of Suvorov, et al., *Zhur. Obsh. Khim.*, 30, 2051-5 (1960); Rodionov, et al., *Zhur. Obsh. Khim.*, 27, 2234-8 (1957); Wasserman, et al., *J. Am. Chem. Soc.*, 105(6), 1697-8 (1983); and Mamaev, *Zhur. Obsh. Khim.*, 27, 1290-3 (1957). It is basically asserted in the Office Action that the compounds taught in the aforementioned publications are encompassed in the Applicants' claims. Applicants respectfully disagree with this rejection and submit that the pending claims define over these references.

In this connection, Applicants' claims define compounds which may be useful in the prophylaxis or treatment of a disease or disorder in which inappropriate protein tyrosine kinase action may play a role. Applicants further teach that compounds according to the present invention may advantageously be potent and selective inhibitors of protein kinases. There is no disclosure whatsoever in the art cited in the Office Action that the compounds disclosed therein may inhibit protein kinases. Indeed, the disclosed compounds are described as being either antithyroidals or intermediates prepared in route to other more complex molecules.

Nevertheless, in order to advance prosecution, claim 1 has been amended in a manner that Applicants believe renders these rejections moot. Particularly, a proviso has been added that stipulates that when Ar^1 is unsubstituted phenyl, r is zero, L^1 is C(O)O, Ar^2 is unsubstituted 1, 4-phenylene or 1,4-phenylene substituted with 3-fluoro, R^a and R^{a1} are hydrogen, and R is CO_2H, then R^3 is other than phenyl. The proviso further stipulates that when r is zero, L^1 is -O-, Ar^2 is 1,4-phenylene substituted with 2-methoxy, R^a and R^{a1} are hydrogen, and R is CO_2CH_3, R^3 is tert-butyloxy, then Ar^1 is other than phenyl substituted in the 4-position with 3-methoxy-3-oxo-1-propenyl. The proviso further stipulates that when Ar^1 is phenyl substituted in the 4-position with methoxy, r is zero, L^1 is -O-, R^3 is methyl, R^a and R^{a1} are hydrogen, and R is CO_2Et, then Ar^2 is other than 3,5-dinitro or 3,5-diiodo substituted. Applicants respectfully submit that in view of these provisos, the claimed compounds further define over the references cited in the Office Action. Under such circumstances, Applicants respectfully request reconsideration and withdrawal of the rejection under Section 102.

Discussion of the Rejections Under Section 112, first paragraph

Claims 17 to 20 have been rejected for containing subject matter not described in such a way as to enable one skilled in the art to make and use the claimed compounds. Applicants respectfully request reconsideration of this rejection as the Office Action fails to establish that it would take anything more than routine experimentation to practice the present invention.

It is well-established that the first paragraph of Section 112 of the patent statute requires only objective enablement of the invention. How the teaching is set forth, either by the use of specific examples or broad terminology, is of no importance. *In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971). Accordingly, when rejecting a claim under the enablement requirement, it is the PTO who bears the initial burden of setting forth technical reasoning as to why it is believed that the scope of protection is not adequately enabled. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *Id.*

Applying these tenets to the present situation, it is respectfully submitted that the present Office Action provides no such technical reasoning to support the opinion that Applicants have not enabled the prevention of any diseases. In fact, the *only* reasoning provided in the Office Action for this conclusion is the unsupported assertion that "[t]he only established prophylactics are vaccines, not the β-amidobenzenepropanoic acid compounds of the present invention." Mere statements, however, are insufficient to compel a conclusion of nonenablement. *In re Colianni*, 668 F.2d 1229 (C.C.P.A. 1982). The statements must be supported by objective evidence. *Id.*

Applicants respectfully submit that in view of the substantial teachings in the specification, the prevention of diseases in which extravasation of leukocytes plays a role is, in fact, enabled. In this connection, Applicants teach that control of the physical interaction of inflammatory leukocytes with each other as well, as with other cell types, plays an important role

in the regulation of immune and inflammatory responses and that these interactions are mediated by specific cell surface molecules including integrins. *See*, for example, page 1, lines 6 to 11 of the specification. Applicants also teach that in one particular subgroup of integrins, the α4 integrins, there is clear evidence that α4β1 (VLA-4) binds to an adhesion molecule known as VCAM-1, which is frequently up-regulated at sites of inflammation. *See*, for example, page 2, lines 17 to 20 of the specification.

Thus, it would be expected by one of ordinary skill in the art that if a VLA-4 inhibitor is given prior to a disease developing, the necessary integrin mediated interactions that lead to the disease are prevented, hence providing a method of prophylaxis. In this connection, Applicants cite the findings of Abraham, et al., *J. Clin. Invest.*, 93 776 (1994) (copy included herewith) on page 2, lines 27 to 28 of the specification, which clearly shows that prophylactic treatment of sheep with an anti-α4 monoclonal antibody prior to antigen challenge inhibits the late-phase increase in specific lung resistance. Given these findings, one would also expect that administration of a small molecule inhibitor of VLA-4 prior to the development of any clinical symptoms would also have a prophylactic effect. Significantly, the Office Action provides no objective evidence suggesting otherwise.

Claims 17 and 18 have also been rejected because, according to the Office Action, Applicants have not enabled the treatment of multiple sclerosis (MS). Despite the statements made in the Office Action, however, Applicants respectfully submit that one of ordinary skill in the art *would* expect Applicants compounds to be of use in the prophylaxis and treatment of MS

based on the teachings provided in the specification. In this connection, Applicants respectfully refer the Examiner to the findings of Yednock, *Nature*, 356, 63 (1992) (copy included herewith), cited by Applicants on page 2, lines 26 of the specification, which demonstrates that in an M.S. animal model (experimental autoimmune encephalomyelitis (EAE)) antibodies against VLA-4 are effective in prevention of EAE. Although the Office Action asserts that the proposed mechanism of action is "still under investigation", Applicants respectfully point out that there is no requirement in the patent laws that a patent specification address all potential problems that might be encountered in practicing an invention. To the contrary, it is improper for the PTO to require any showing regarding the degree of effectiveness of therapeutic inventions, such as those now claimed. M.P.E.P. § 2107.02; *In re Sichert,* 566 F.2d 1154 (C.C.P.A. 1977).

Nevertheless, the Office Action questions the degree to which the claimed compounds would show efficacy in MS based on the findings of Noseworthy, *Nature*, Vol. 399, 40-47 (1999) (the first Noseworthy reference). Applicants respectfully disagree. The mere fact that the Noseworthy reference suggests that adhesion molecule signaling may constitute a future therapeutic strategy in no way calls into questions the enablement of Applicants' invention. The only support for this conclusion provided in the Office Action is that the first Noseworthy reference is "implying" that mechanistic approaches like Applicants have not demonstrated efficacy. Applicants respectfully submit, however, that subjective implication does not constitute the type of well-reasoned, objective evidence required to support the current rejection under Section 112, first paragraph.

The Office Action also cites Noseworthy, et al., *Curr. Opin. Neurology*, 12, 279-293 (1999) (the second Noseworthy reference) as purportedly demonstrating that Applicants' mechanistic approach has "led to severe side effects." What the present Office Action fails to recognize is that these statements were made in connection with the testing of an ***antibody*** to α4 integrins. As such, the purported "side effects" have absolutely no relationship to the claimed compounds as these effects could be related to any number of different factors not connected to the anti-VLA-4 activity.

Regardless, even assuming, *arguendo*, that the presently claimed compounds did display side effects, this fact alone would not negate their patentablility. Indeed, such problems are actually to be expected. It is well-established that pharmaceutical inventions usually require further research and development. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Were such inventions not patentable long before being optimized or ready for human use, the incentive to fully research and develop vital drugs and potential cures would be completely removed. *Id.* at 1567-68. Applicants, however, have provided, for example, on page 54, line 23 to page 56, line 27 of the specification, assays that may be used to determine biological activity and specificity together with the levels for activity that are preferably obtained for the compounds to be suitable for the claimed use. Because the Office Action provides no credible reason for doubting that compounds possessing activity would be useful in treating MS to some measurable extent, Applicants respectfully request reconsideration and withdrawal of the rejection under Section 112, first paragraph.

Rejections Under Section 112, second paragraph

The Office Action includes various objections to the form of Applicants' claims accompanied by a statement that the claims are indefinite. It is submitted respectfully that one of ordinary skill in the art would have no difficulty in understanding the metes and bounds of Applicants' original claims, and the terminology used therein, as they are both clear and definite.

The term "solvates" has been objected to as reading on an unlimited and undefined number of solvent complexes. Applicants respectfully submit, however, that the Office Action confuses breadth with indefiniteness as one of ordinary skill in the art would have no difficulty appreciating the meaning and scope of the term. For example, solvates may be formed by reversible combination of a claimed compound with any solvent that may be used, for example, during the course of synthesis. Although numerous solvents are possible, that fact in no way confuses the skilled artisan as to what is meant by the term "solvates." Thus, requiring Applicants to specifically enumerate such solvents would not only be unnecessary for an appreciation of the term, but would serve only to needlessly limit Applicants' invention.

The use of the term "heteroatom-containing group" in the definition of Alk^a has been objected to because, according to the Office Action, it is unclear which groups Applicants intended. Although Applicants certainly disagree that these terms lack definiteness, to facilitate prosecution these terms have been amended in claim 16 to recite that the heteroatom-containing groups are selected from selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $N(R^8)$ (where R^8 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group),

-C(O)NR^8-, -OC(O)N(R^8)-, -CSN(R^8)-, -N(R^8)CO-, -N(R^8)C(O)O-, -N(R^8)CS-, -S(O)$_2$N(R^8)-, -N(R^8)S(O)$_2$-, -N(R^8)CON(R^8)-, -N(R^8)CSN(R^8) and N(R^8)SO$_2$N(R^8).

The Office Action asserts that the term "optionally substituted" is not understood inasmuch as it is unclear what substituents are encompassed by the claims and where they reside. Applicants respectfully point out that the present invention relates to novel phenylalanine derivatives possessing desirable biological activity. It will therefore be appreciated by one of ordinary skill in the art that the biological activity would be expected to be maintained despite the specific nature of the substituent groups. In any event, the claims must be read in view of the specification and Applicants have exemplified optional substituents therein. Indeed, optional substituents for Ar^1 are provided, for example, on page 7, line 5 to page 9, line 36 of the specification and optional substituents for aliphatic and heteroaliphatic groups are provided, for example, on page 10, line 27 to page 11, line 3 of the specification. With respect to the assertion that it is somehow unclear where such substituents are to be placed, Applicants respectfully submit that this would be immediately apparent to one of ordinary skill in the art. For example, the term "optionally substituted aromatic group" would be understood by the skilled artisan to mean that the hydrogens of the aromatic ring may be substituted with additional groups, such as, for example, the representative groups provided in the specification.

The Office Action objects to various terms used in the claims including "heteroatoms", "heteroaromatic", "heteroaliphatic", "cycloaliphatic", "heterocycloaliphatic", "polycycloaliphatic", and "heteropolycycloaliphatic." It is basically asserted that one of ordinary

skill in the art would not recognize which atoms are intended or which groups are encompassed by these terms. Applicants respectfully submit, however, that one of ordinary skill in the art would, in fact, have no difficulty understanding the terminology used in the description or the metes and bounds of Applicants' amended claims.

Applicants note that a fundamental principle of Section 112, second paragraph, is that the Applicants are their own lexicographers and may define the claims in whatever terms they so choose. M.P.E.P. §2173.01. Accordingly, a claim may not be rejected solely because of the type of language used to define the subject matter. *Id*; *see also*, *In re Swinehart*, 439 F.2d 210 (C.C.P.A. 1971). The definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure and the claim interpretation that would be given by one possessing the ordinary level of skill in the art. *In re Marosi*, 710 F.2d 799 (Fed. Cir. 1983).

Applying these rules to the present rejection, Applicants respectfully submit that the Office Action utterly fails to take into account not only the level of skill in the art, but also the specific definitions provided in the specification. Instead, the Office Action attempts to reserve the right to select the claim language for the Patent Office. This is evidenced by the suggestion that the aforementioned terms are "improper" and "oxymorons" followed by recommended terms the Examiner subjectively finds more agreeable. Applicants respectfully decline to adopt the recommended terms, however, as they are under no obligation to do so under

the patent laws. Alternatively, Applicants' have elected, for purposes of clarity, to amend claim 16 in a manner consistent with the specification to address the Examiner's concerns.

In this connection, the variables "heteroaliphatic", "heterocycloaliphatic", heteropolycycloaliphatic" have been amended to recite that heteroatoms or heteroatom-containing groups are selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$ (where R^8 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group), $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$ and $-N(R^8)SO_2N(R^8)-$. Additionally, the variable "heteroaromatic" has been amended to recite that the group contains one to four heteroatoms selected from O, N, and S.

The Office Action states that the expression "heteroaliphatic containing one, two, three, or four heteroatoms is particularly troublesome." As best understood, this expression is considered troublesome in that, according to the Office Action, neither the nature of the heteroatoms nor their location in the aliphatic chain is understood. Without commenting on the propriety of this statement, Applicants respectfully point out that claim 16 has now been amended to indicate that the heteroatoms are O, N, and S. With respect to the assertion that it is unclear as to whether the heteroatoms are intended as substituents, or to interrupt the chain, Applicants respectfully submit that it would be clear to one of ordinary skill in the art that the heteroatoms interrupt the chain, namely, because this is the only chemical possibility. Heteroatoms are not substituents. Moreover, if the Office Action were correct that alkoxy and

NR^dR^e were encompassed this definition, the term "optionally substituted", which precedes this variable in certain situations, would be redundant.

The Office Action also objects to the phrase "carboxylic acid, or an ester or amide" as indicating compounds, not radicals. For purposes of clarity, Applicants have amended claim 16 to indicate that carboxylic acid signifies CO_2H, and that the amide and ester moieties are groups, not independent molecules.

Claim 17 stands rejected because, according to the Office Action, the phrase "a disease or disorder in a mammal in which the extravascation [sic, extravasation] of leukocytes plays a role" is indefinite because it is unclear which diseases are intended and how much of a role the leukocyte must play. Applicants respectfully disagree that claim 17 is in any way unclear. To the contrary, on page 22, lines 8 to 11 of the specification, Applicants exemplify which diseases involve inappropriate leukocyte extravasation. Thus, Applicants respectfully assert that the statement in the Office Action that "extensive research" would be necessary to discover in which diseases leukocytes play a role, is plainly incorrect. To the contrary, in view of the specification, claim 17 is both clear and definite.

In view of the above amendments and remarks, reconsideration and withdrawal of the rejection under Section 112, second paragraph, is requested respectfully.

Rejection Under Section 101

Claims 21 and 22 have been rejected because, according to the Office Action, neither a specific, substantial[1], nor well-established utility supports the claimed invention. Applicants, however, are at a loss to understand how this conclusion could be reached not only in view of the extensive teachings provided, for example, on pages 1 to 3 of the specification, but the apparent recognition in the Office Action that inhibition of α4 binding results in the prophylaxis and treatment of immune or inflammatory disorders. Applicants also note that claims 21 and 22 have also been rejected under Section 112, first paragraph, presumably by virtue of their rejection under Section 101. It is unclear however, how the Office Action can simultaneously state that the specification enables the treatment of diseases in claims 17 to 20 (*i.e.*, teaches how to "use" the invention), and then allege that the use of the invention is not specific or well-established for claims 21 and 22.

As best understood, the rationale for this inconsistency is that claims 21 and 22 are not "drawn to a disease", that is, do not specifically recite a disease in the claim. Applicants know of no authority, however, that requires each and every claim to specifically recite the utility to satisfy Section 101. To the contrary, compound claims, for example, claim 16, rely on the specification to inform the public of at least one utility of the invention. In view of Applicants' specification, it is respectfully submitted that the Office Action is somewhat disingenuous when

[1] Applicants are unclear as to what is meant by "substantial utility." To the extent the rejection is maintained beyond Applicants' traversal, clarification is respectfully requested.

it posits the question "[w]hat is the purpose of 'inhibiting, in a mammal, the binding of α4 integrins to the ligands thereof, [with] a compound of claim 16'?" The answer to this question is presented on pages 1 to 3 of the specification where Applicants state "with specificity" that the inhibition of α4 binding results in, *inter alia*, the prophylaxis and treatment of immune or inflammatory disorders.

With respect to the allegation that this utility is not "well-established," Applicants respectfully point out that if the asserted utility of a compound is credible on its face to persons skilled in the art, then a rejection for lack of utility is inappropriate. M.P.E.P §706.03(a)(1). Credibility is to be assessed in view of any evidence of record that is relevant to Applicants' assertions. *Id.* In the present situation, Applicants' specification contains extensive teachings such that one of ordinary skill in the art would conclude that the logic underlying Applicants' asserted utility is not seriously flawed, and that the facts upon which the assertion is based, and the underlying logic, are not inconsistent. Because the Office Action presents no reasons for concluding otherwise, Applicants respectfully request that the rejection under Section 101 be reconsidered and withdrawn.

Miscellaneous

Support for the amendments to claim 16 is provided, for example, on page 6, lines 5 to 8 and lines 15 to 18; page 7, lines 24 to 32; page 10, lines 7 to 13; page 11, lines 11 to 16 and 20 to 23; page 13, lines 8 to 12.

The Office Action indicates that the references cited in the Information Disclosure Statement filed by Applicants on January 14, 2000 have not been considered because "they are all missing." Accordingly, Applicants enclose herewith 1) a copy of the original postcard accompanying the Information Disclosure Statement indicating that 91 references were submitted to the Patent and Trademark Office; and 2) a copy of the returned postcard stamped "received" by the Patent and Trademark Office on January 14, 2000.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable reconsideration of the rejections and an allowance of the pending claims is requested respectfully.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 16 has been amended as follows.

16. (amended once) A compound of formula (1):

$$Ar^1(Alk^a)_rL^1Ar^2CH(R^1)C(R^a)(R^{a'})R \qquad (1)$$

wherein

Ar^1 is an optionally substituted aromatic or C_{1-9} heteroaromatic group containing one to four heteroatoms seleted from oxygen, nitrogen, and sulfur;

L^1 is a covalent bond or a linker atom or group selected from $-CON(R^2)-$, $-S(O)_2N(R^2)$, $-C(O)O-$, $-N(R^2)-$, [or] and $-O-$;

R^2 is a hydrogen atom or a C_{1-3} alkyl group;

Ar^2 is an optionally substituted phenylene group;

R^1 is a group selected from $-NHCOR^3$, $-NHSO_2R^3$, $-NHR^3$, $-NHC(O)OR^3$, $-NHCSR^3$, $-NHCON(R^3)(R^{3a})$, $-NHSO_2N(R^3)(R^{3a})$ [or] , and $-NHCSN(R^3)(R^{3a})$;

R^3 is an optionally substituted C_{1-6} aliphatic group, an optionally substituted C_{1-6} heteroaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$ (where R^8 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group), $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$ and $-N(R^8)SO_2N(R^8)-$;[,] an optionally substituted C_{3-10}

cycloaliphatic group, an optionally substituted C_{7-10} polycycloaliphatic group, an optionally substituted C_{3-10} heterocycloaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$ and $-N(R^8)SO_2N(R^8)-$; [,] an optionally substituted C_{7-10} heteropolycycloaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$ and $-N(R^8)SO_2N(R^8)-$; [,] an optionally substituted aromatic group, or an optionally substituted C_{1-9} heteroaromatic group containing one, two, three or four heteroatoms seleted from oxygen, nitrogen, and sulfur; [or heteroatom-containing groups];

R^{3a} is a hydrogen atom, an optionally substituted C_{1-6} aliphatic group, an optionally substituted C_{1-6} heteroaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$ and $-N(R^8)SO_2N(R^8)-$;[,] an optionally substituted C_{3-10} cycloaliphatic group, an optionally substituted C_{7-10} polycycloaliphatic group, an optionally substituted C_{3-10} heterocycloaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-,

-C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -$N(R^8)$-, -$C(O)NR^8$-, -$OC(O)N(R^8)$-, -$CSN(R^8)$-, -$N(R^8)CO$-, -$N(R^8)C(O)O$-, -$N(R^8)CS$-, -$S(O)_2N(R^8)$-, -$N(R^8)S(O)_2$-, -$N(R^8)CON(R^8)$-, -$N(R^8)CSN(R^8)$-, and -$N(R^8)SO_2N(R^8)$-;[,] an optionally substituted C_{7-10} heteropolycycloaliphatic group containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, -$S(O)_2$-, -$N(R^8)$-, -$C(O)NR^8$-, -$OC(O)N(R^8)$-, -$CSN(R^8)$-, -$N(R^8)CO$-, -$N(R^8)C(O)O$-, -$N(R^8)CS$-, -$S(O)_2N(R^8)$-, -$N(R^8)S(O)_2$-, -$N(R^8)CON(R^8)$-, -$N(R^8)CSN(R^8)$- and -$N(R^8)SO_2N(R^8)$-;[,] an optionally substituted aromatic group, or an optionally substituted C_{1-9} heteroaromatic group containing one, two, three or four heteroatoms seleted from oxygen, nitrogen, and sulfur; [or heteroatom-containing groups];

R^a and $R^{a'}$, which may be the same or different, are each independently selected from a hydrogen or halogen atom or an optionally substituted straight or branched alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, alkylthio or $-(Alk^b)_mR^b$ group (in which Alk^b is a C_{1-3} alkylene chain, m is zero or the integer 1, and R^b is -OH, -SH, -NO_2, -CN, -CO_2H, -CO_2R^c (where R^c is an optionally substituted straight or branched C_{1-6} alkyl group), -SO_3H, -SOR^c, -SO_2R^c, -SO_3R^c, -OCO_2R^c, -C(O)H, -$C(O)R^c$, -$OC(O)R^c$, -$C(S)R^c$, -NR^dR^e (where R^d and R^e, which may be the same or different, are each a hydrogen atom or an optionally substituted straight or branched C_{1-6} alkyl group), -$CON(R^d)(R^e)$, -$OC(O)N(R^d)(R^e)$, -$N(R^d)C(O)R^e$, -$CSN(R^d)(R^e)$, -$N(R^d)C(S)R^e$, -$S(O)_2N(R^d)(R^e)$, -$N(R^d)SO_2R^e$, -$N(R^d)CON(R^e)(R^f)$ (where R^f is a hydrogen atom

or an optionally substituted straight or branched C_{1-6} alkyl group), $-N(R^d)C(S)N(R^e)(R^f)$ or $-N(R^d)SO_2N(R^e)(R^f)$ group);

Alk^a is an optionally substituted C_{1-6} aliphatic or C_{1-6} heteroaliphatic chain containing one, two, three or four heteroatoms or heteroatom-containing groups selected from -O-, -S-, -C(O)-, -C(O)O-, OC(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^8)-$, $-C(O)NR^8-$, $-OC(O)N(R^8)-$, $-CSN(R^8)-$, $-N(R^8)CO-$, $-N(R^8)C(O)O-$, $-N(R^8)CS-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, $-N(R^8)CON(R^8)-$, $-N(R^8)CSN(R^8)-$, and $-N(R^8)SO_2N(R^8)-$;

r is zero or the integer 1;

R is a carboxylic acid (CO_2H), or an ester group or amide group;

and the salts, solvates, hydrates and N-oxides thereof[.];

with the provisos that:

(1) when Ar^1 is unsubstituted phenyl, r is zero, L^1 is C(O)O, Ar^2 is unsubstituted 1, 4-phenylene or 1,4-phenylene substituted with 3-fluoro, R^a and $R^{a'}$ are hydrogen, R is CO_2H, and R^1 is $NHCOR^3$, then R^3 is other than unsubstituted phenyl;

(2) when r is zero, L^1 is -O-, Ar^2 is 1,3-phenylene substituted with 4-methoxy, R^a and $R^{a'}$ are hydrogen, and R is CO_2CH_3, R^1 is $NHCOR^3$, R^3 is tert-butyloxy, then Ar^1 is other than phenyl substituted in the 4-position with 3-methoxy-3-oxo-1-propenyl; and

(3) when Ar^1 is phenyl substituted in the 4-position with methoxy, r is zero, L^1 is -O-, R^1 is $NHCOR^3$, R^3 is methyl, R^a and $R^{a'}$ are hydrogen, and R is CO_2Et, then Ar^2 is other than 3,5-dinitro or 3,5-diiodo substituted.